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A Retrospective Occupational Cohort Study of End-Stage Renal Disease in Aircraft Workers Exposed to Trichloroethylene and Other Hydrocarbons

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Learning Objectives

- Outline the apparent association between the risk of end-stage renal disease (ESRD) in aircraft workers and occupational exposure to trichloroethylene and other hydrocarbons.
- State the ways, if any, in which the association between hydrocarbon exposure and ESRD is influenced by age, race, and gender.
- Provide explanations for, and implications of, the findings of this occupational study of ESRD and hydrocarbons.

Abstract

Objective: *Case–control studies suggest hydrocarbons increase end-stage renal disease (ESRD) risk. No cohort studies have been conducted.* ***Methods:*** *An occupational database was matched to the U.S. Renal Data System, and the outcome of all-cause ESRD was examined using multivariable Cox regression. Sixteen individual hydrocarbons were studied, although exposures were not mutually exclusive.* ***Results:*** *For the 1973–2000 period, there was an approximate twofold increased risk of ESRD among workers exposed to trichloroethylene, 1,1,1-trichloroethane, and JP4 gasoline compared with unexposed subjects (all* $P < 0.05$*). Relative risk was greater than unity (*$P > 0.05$*) for several other hydrocarbons. Associations attenuated (all* $P > 0.05$*) when 2001–2002 data were included in the analyses.* ***Conclusions:*** *Certain hydrocarbons may increase all-cause ESRD risk. Uncertainty regarding the mechanism for increased risk and the observed attenuation in risk in 2001–2002, as well as the overlap of exposures, complicates interpretation. Additional research is needed.* (J Occup Environ Med. *2006;48:1–12*)

End-stage renal disease (ESRD) is an important public health problem in the United States. The U.S. Renal Data System (USRDS) reported that in 2001, there were 406,081 cases of ESRD prevalent in the United States and over 96,000 incident cases.[1] The disease has become more common with the age-adjusted annual incidence rate increasing nearly 53% between 1991 and 2001—from 219 to 334 per million per year. ESRD represents a large and growing economic burden to society. In 2001, ESRD costs consumed 6.4% ($15.4 billion) of the entire Medicare budget.[1]

Patients with ESRD have chronic renal failure (CRF) that has advanced to the point that they require either chronic dialysis or a renal transplant to survive. Although much is known about the systemic causes of CRF such as diabetes and hypertension, rather little is known about its possible occupational or environmental causes. Wedeen has discussed the potential for occupational exposures such as heavy metals and hydrocarbons to cause renal disease.[2] Identification of potential occupational causes of CRF is challenging because of the complex multifactorial etiology of the disease (a likely combination of systemic diseases, toxins, nutritional factors, and genetics), the time lag between exposure and disease, and the nonspecific nature of the renal histopathology once it advances to the end stage. The occupational etiology of acute renal failure, in con-

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DOI: 10.1097/01.jom.0000190300.51629.e0

trast, is often quite apparent because of the readily identifiable circumstances that precede the onset of disease such as massive accidental exposure to toxins from ingestion, immersion, or inhalation.[2]

The scientific understanding of the relationship between hydrocarbon exposure and chronic renal disease has progressed slowly. Nelson et al reviewed six case–control studies in 1990 and found that, despite possible methodological limitations in some of the studies such as lack of interviewer masking and/or recall bias, the studies were relatively consistent in reporting an association between hydrocarbon exposure and glomerulonephritis—one of the main causes of ESRD.[3] A decade later, Ravnskov conducted a meta-analysis of 14 case–control studies and reported that the combined data support the hypothesis that hydrocarbon exposure increases the risk of chronic renal disease.[4] Specific hydrocarbons were not identified in these reviews. It is challenging to study the effects of individual hydrocarbons on disease outcomes because most higher exposures occur in occupational settings, and these exposures are commonly a mixture of aromatic and nonaromatic and chlorinated and nonchlorinated compounds.

The hydrocarbon trichloroethylene (TCE) is an industrial solvent that has been used in the past in numerous occupational settings, most notably as a metal degreaser.[5] In addition to occupational exposure, environmental exposure is possible because the high utilization of TCE over the years has resulted in widespread soil and groundwater contamination across the United States. Of the 1428 toxic waste sites comprising the Environmental Protection Agency's National Priorities List (NPL) in the late 1990s, TCE had been found at more than half.[6]

Because individuals with ESRD have been shown to have an increased likelihood of exposure to hydrocarbons in case–control studies and because TCE is a relatively common occupational exposure and environmental contaminant, we thought it would be valuable to conduct a study on the association between TCE and ESRD using, for the first time that we are aware of, a retrospective cohort design.

Materials and Methods

Data Sources

Our study used data from three sources: a database of former civilian employees of the Hill Air Force Base in Utah, mortality data from the National Death Index (NDI), and ESRD incidence data from the U.S. Renal Data System (USRDS) database.

Hill Air Force Base. The Hill Air Force Base occupational cohort has been described in detail previously.[7–9] Briefly, in the early 1980s, the National Cancer Institute (NCI) assembled this cohort with the objective of studying the health impact of occupational exposure to organic solvents and, in particular, TCE. The cohort comprises all civilians employed at the aircraft maintenance facility for at least 1 year between January 1, 1952, and December 31, 1956. Data on date of birth, race, and gender and a complete work history at the base were extracted from the personnel records. Data were also collected from death records on the date and the underlying and contributing causes of death, and these were coded according to the Eighth Revision of the International Classification of Diseases (ICDA-8). The cohort included 14,455 workers, of which approximately one half had been exposed to TCE. In an effort to provide a semiquantitative estimate of TCE exposure, a comprehensive exposure assessment effort was carried out by the NCI. Because TCE was the primary chemical of interest at the outset of the study, a more detailed evaluation was conducted for this hydrocarbon. As an estimate of intensity of exposure, a cumulative exposure score for TCE was computed for each subject based on frequency (times/d), duration (min/d), calendar period of use, and years of exposure and is described in detail elsewhere.[8] Categories of exposure (eg, continuous or intermittent) were also estimated for TCE, 1,1,1-trichloroethane, and mixed solvents (defined as exposure to one or more solvents) and have been described previously.[8] Data were also available for all workers regarding exposure to other hydrocarbons used at the base (yes/no and years of exposure).

National Death Index. The NDI, administered by the National Center for Health Statistics (NCHS), is a central computerized index of death record information for the entire United States beginning with deaths reported in 1979.[10] The NDI Plus contains underlying and contributing cause of death codes using the Ninth Revision of the International Classification of Diseases (ICD-9) for the years 1979–1998 and the Tenth Revision of the International Classification of Diseases (ICD-10) for 1999 and later.

U.S. Renal Data System. The USRDS, which is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in conjunction with the Centers for Medicare and Medicaid Services (CMS), collects, analyzes, and distributes information about ESRD in the United States.[11] Incidence data are available from approximately 1973 onward. The USRDS receives its ESRD information on patients from the CMS Renal Beneficiary and Utilization System (REBUS), which was adopted in 1995 as the On-Line Transaction Processing system from the previous Program Management and Medical Information System (PMMIS) database. The PMMIS/REBUS database contains demographic, diagnostic, and treatment history data for all Medicare beneficiaries with ESRD, and in 1995, the database was expanded to include non-Medicare patients. Validation studies of the USRDS have reported that the database is relatively complete and reliable—capturing approximately 95% of actual ESRD cases and achieving

approximately 90% agreement with source documents and other databases on key variables.[12,13]

Data Analysis

Matching of Data Files. The cohort was first matched to the NDI using available personal identifiers (ie, name, social security number, gender, race, and date of birth) to assess survival status between 1991 and 2000. A previous study of the cohort by Blair et al had reported survival status through 1990.[9] Data on age at death was necessary for censoring subjects in our Cox proportional hazards regression models—when subjects died, they were no longer at risk for ESRD and ceased contributing person-time to the denominator of the incidence rate. Second, we matched the cohort to the USRDS to identify ESRD cases and age at first ESRD treatment. The cause of death data from the earlier follow-up studies[7,9] and our NDI match could not be used to identify subjects who might have died from ESRD, and not been captured by the USRDS, because there were no ICDA-8 or ICD-9 codes for ESRD. There is an ICD-10 code for ESRD (N18.0); however, there were no deaths in our cohort with this particular code listed as the underlying cause.

Hydrocarbons. We analyzed risk of ESRD from possible exposure to 16 individual hydrocarbons used at the Hill Air Force Base as well as mixed solvents. The specific hydrocarbons evaluated were: TCE, 1,1,1-trichloroethane, methylene chloride, carbon tetrachloride, JP4 gasoline, Freon, isopropyl alcohol, acetone, toluene, methylethyl ketone, O-dichlorobenzene, perchlorethylene, chloroform, Stoddart solvent, styrene, and xylene.

Statistical Analysis. When we conducted our matches with the USRDS and the NDI, ESRD data were available from the USRDS from 1973 through September 30, 2002; however, mortality data were available from the NDI through December 31, 2000, only. We used a Cox proportional hazards regression model to estimate the relative risk of ESRD for Hill Air Force Base subjects exposed to hydrocarbons for the period 1973 through 2000—the years for which both ESRD and death data were available. To analyze all the ESRD data we received from the USRDS, however, we used a logistic regression model for the period 1973 through 2002. The Cox model, which computes a hazard ratio as a function of time, was not appropriate for analysis of the full follow-up period (1973 through 2002) because we could not censor subjects who may have died in 2001 and 2002.

We ran both univariable and multivariable Cox and logistic regression models with ESRD as the dependent variable. As recommended in the literature, we selected age as the time variable in the Cox model because disease and death rates usually change rapidly with age, and age effects should be controlled as precisely as possible.[14,15] In conducting the analyses, we forced race and gender into the regression models and also ran separate analyses stratified by these two variables, because race (black) and gender (male) are known risk factors for ESRD.[1] Because calendar year and length of follow up can be predictors of disease in occupational studies, it has been recommended that adjustments be made for both variables.[15] Therefore, we ran the multivariable Cox model stratified by 5-year calendar bands (<1980, 1981–1985, 1986–1990, 1991–1995, and 1996–2000) and by 5-year follow-up bands (1–5, 6–10, 11–15, 16–20, 21–25, and 26–30). In addition, to examine if and how early in the follow up ESRD risk may have been increased for hydrocarbon-exposed subjects, we computed hazard ratios for different calendar time periods, starting with 1973 through 1975 (1973 was the first year ESRD incidence data were available from the USRDS and 1975 was the first ESRD case in our cohort) and then increasing the interval 2 years at a time. We also ran our multivariable Cox model for the subgroup of subjects less than age 60 to assess whether the relative risk differed for individuals of working age who would more likely be currently or recently exposed to hydrocarbons compared with older, retired members of the cohort.

For analyses of TCE and the other hydrocarbons, we selected subjects who had either been exposed to the chemical of interest or who were never exposed to any chemicals (referent group). Because exposed cohort subjects usually worked with more than one chemical, there was overlap in exposures and we could not assess risk for individual hydrocarbons while controlling for other chemicals.

We tested for first-order interactions in the Cox models by including crossproduct terms for any covariates that were statistically significant ($P < 0.05$) in the multivariable model. We also calculated unadjusted odds ratios and 95% confidence intervals using a 2×2 table approach and presented these results alongside the regression model results to assess the degree of confounding present and provide some assurance that the regression model results were valid.

To evaluate exposure–response, we ran the Cox model with the TCE cumulative exposure score, which had been developed earlier by the study industrial hygienists.[8] For analysis, the score was categorized into tertiles: less than 5 unit years, 5 to 25 unit years, greater than 25 unit years, and a Mantel linear trend test was carried out. We also ran the model for the specified categories of exposure that had been used in calculating the TCE cumulative exposure score and which have been described in detail previously[8]—peak exposure (frequent or infrequent) and low exposure (continuous or intermittent). These were further categorized into direct or indirect exposure. The study industrial hygienists had also developed specified

categories for mixed solvents (continuous or intermittent, further categorized into direct or indirect) and for 1,1,1-trichloroethane (direct or indirect), which we were able to analyze. Although such detailed exposure data were not available for any of the other hydrocarbons used at the base, we had person-years of exposure with which to assess exposure–response for TCE, mixed solvents, and all the other hydrocarbons. For these analyses, we categorized person-years into tertiles and conducted a Mantel linear trend test.

We also carried out an analysis to assess whether observed associations, if any, could be the result of differences between the exposed and unexposed groups in socioeconomic status (SES). SES is a well-established risk factor for many diseases[16] and has been reported to be an independent risk indicator specifically for chronic renal disease.[17] Spirtas et al noted that the proportion of Hill Air Force Base workers with no chemical exposure who were salaried was 61% compared with less than 1% of the exposed workers being salaried,[7] suggesting higher SES was strongly correlated with lower exposure. To see if the exposed and unexposed groups in the cohort differed in risk of diseases with known SES gradients, cardiovascular disease,[16] diabetes,[16] and chronic liver disease and cirrhosis,[18] which are not believed to be associated with hydrocarbon exposure,[19–21] we computed death rates and adjusted hazard ratios for these three diseases (for cardiovascular disease, we looked specifically at ischemic heart disease). Associations have been reported in the literature for certain hydrocarbons and ischemic heart disease, most notably carbon disulfide[19] and styrene,[22] but the former was not known to be used at the base[9] and less than 2% of workers who worked with hydrocarbons used styrene. Also, although hydrocarbon exposure might be associated with liver disease,[23] we included in our analysis only diagnoses of chronic liver disease and cirrhosis that mentioned alcohol specifically (we labeled this alcoholic liver disease).

Ethical Review and Subject Confidentiality. The study was reviewed and approved by the Institutional Review Boards at the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School and the U.S. Air Force (USAF). Approvals/permissions were also obtained from the NCI, the NDI, and the USRDS. The Hill Air Force Base Union was notified about the study. All personal identifiers within the final analytic data file were deleted and destroyed before conducting statistical analyses.

Software. All statistical analyses were performed using SPSS statistical software, version 11.0, developed by SPSS Inc., Chicago, Illinois.

Results

The Hill Air Force Base cohort (n = 14,455) comprises 10,730 male (74.2%) and 3725 female subjects (25.8%), of which 12,537 are white (86.7%), 390 are nonwhite (2.7%), and 1528 are of unknown race (10.6%). Like in the previous studies of the cohort by Spirtas et al[7] and Blair et al,[9] workers of unknown race were classified as white because those of known race were overwhelmingly white (97%). We also examined the risk of ESRD in the white, nonwhite, and unknown race populations and found that white subjects and subjects of unknown race had comparable ESRD risks (0.6% and 0.7%, respectively) but that the risk in nonwhite subjects was greater (2.3%). This is consistent with the known excess risk of ESRD in blacks.[1] The mean age of the 5875 (40.6%) subjects still alive as of December 31, 2000, was 75 years (standard deviation [SD] = 7). There were 86 cases of ESRD identified through December 31, 2000, and an additional 15 cases were identified in 2001 and 2002. Of the 101 total ESRD cases, 34 were reported by the USRDS to be caused from diabetes, 23 from hypertension, 11 from glomerulonephritis, and 33 subjects had other, unknown, or missing causes. We ran our analyses for the 12,421 subjects still alive as of January 1, 1973, because that was the first year ESRD incidence data were available from the USRDS, and we included all cases of ESRD regardless of cause (we could not conduct cause-specific analyses because of small numbers).

In our 2 × 2 table univariable analyses of the association between hydrocarbons and ESRD, we found several statistically significant increased odds ratios for the period 1973 through 2000, including ones for TCE, 1,1,1-trichloroethane, methylene chloride, carbon tetrachloride, Stoddart solvent, JP4 gasoline, and mixed solvents (Table 1). The univariable Cox model provided similar results as the 2 × 2 table analyses, and in addition, the increased relative risk for acetone was statistically significant. Associations for TCE, 1,1,1-trichloroethane, and JP4 gasoline remained statistically significant in the multivariable Cox model. Risks were elevated, although not statistically significant, for several other hydrocarbons in the multivariable Cox model, including methylene chloride, O-dichlorobenzene, acetone, xylene, isopropyl alcohol, Freon, chloroform, carbon tetrachloride, Stoddart solvent, styrene, and mixed solvents. There were no statistically significant interactions.

In Table 2, the gender-specific Cox model results for the 1973 through 2000 period are presented for TCE, 1,1,1-trichloroethane, and JP4 gasoline. Although the numbers were small and none of the associations were statistically significant for males or females, the hazard ratio point estimates for both were similar. Thus, women as well as men appeared to be at increased risk of ESRD from hydrocarbon exposure. There were too few nonwhite subjects exposed to hydrocarbons to conduct robust race-specific analyses. When we ran the multivariable

TABLE 1
Total Number of ESRD Cases (total number exposed), Number of Exposed ESRD Cases, and Results of 2 × 2 Table Analyses and Unadjusted and Adjusted Cox Regression Analyses by Hydrocarbon Exposure, With 95% Confidence Intervals, 1973–2000 Period

Exposure	Total No. of ESRD Cases (total no. exposed)	No. of Exposed ESRD Cases	2 × 2 Table-Unadjusted OR and (95% CI) 1973–2000	Cox Regression Unadjusted HR and (95% CI) 1973–2000	Cox Regression Adjusted* HR and (95% CI) 1973–2000
Trichloroethylene	71 (6,532)	56	**1.91 (1.08–3.38)**	**1.97 (1.11–3.48)**	**1.86 (1.02–3.39)**
1,1,1-trichloroethane	37 (2,188)	22	**2.24 (1.16–4.33)**	**2.44 (1.26–4.72)**	**2.31 (1.04–5.10)**
Methylene chloride	26 (1,099)	11	**2.23 (1.02–4.88)**	**2.39 (1.10–5.20)**	2.18 (0.93–5.11)
O-dichlorobenzene	21 (834)	6	1.60 (0.62–4.14)	1.71 (0.66–4.41)	1.78 (0.63–5.08)
Acetone	32 (2,030)	17	1.87 (0.93–3.74)	**2.01 (1.01–4.03)**	1.73 (0.82–3.63)
Toluene	24 (1,669)	9	1.20 (0.52–2.74)	1.21 (0.53–2.76)	1.06 (0.45–2.50)
Xylene	16 (81)	1	2.76 (0.36–21.15)	2.68 (0.35–20.25)	1.76 (0.22–14.23)
Methylethyl ketone	22 (1,533)	7	1.01 (0.41–2.49)	1.03 (0.42–2.54)	0.92 (0.36–2.33)
Isopropyl alcohol	32 (2,154)	17	1.76 (0.88–3.53)	1.94 (0.97–3.89)	1.91 (0.87–4.19)
Other alcohols	18 (694)	3	0.96 (0.28–3.32)	1.00 (0.29–3.44)	1.05 (0.28–3.96)
Freon	30 (2,235)	15	1.49 (0.73–3.06)	1.62 (0.79–3.33)	1.63 (0.72–3.69)
Chloroform	18 (240)	3	2.80 (0.80–9.72)	3.08 (0.89–10.67)	2.66 (0.71–10.05)
Carbon tetrachloride	64 (5,974)	49	**1.83 (1.02–3.26)**	**1.89 (1.06–3.36)**	1.76 (0.96–3.22)
Perchloroethylene	18 (593)	3	1.12 (0.32–3.89)	1.12 (0.32–3.86)	0.97 (0.27–3.52)
Stoddart solvent	64 (6,102)	49	**1.79 (1.00–3.19)**	**1.87 (1.05–3.34)**	1.65 (0.90–3.03)
Styrene	17 (156)	2	2.87 (0.65–12.65)	2.79 (0.64–12.18)	2.74 (0.61–12.30)
JP4 gasoline	47 (3,285)	32	**2.17 (1.17–4.02)**	**2.31 (1.25–4.28)**	**2.26 (1.16–4.41)**
Mixed solvents	84 (8,816)	69	**1.74 (1.00–3.05)**	**1.77 (1.02–3.10)**	1.60 (0.89–2.88)

Values in bold are statistically significant ($P < 0.05$).
*Multivariable Cox regression model: time variable = age; covariates include race and gender.
Referent group for all comparisons = subjects with no chemical exposure (n = 3,327).
OR indicates odds ratio; HR, hazard ratio; CI, confidence interval; ESRD, end-stage renal disease.

TABLE 2
Gender-Specific Total Number of ESRD Cases (total number exposed), Number of Exposed ESRD Cases, and Results of Adjusted Cox Regression Analyses by Selected Hydrocarbon Exposure, With 95% Confidence Intervals, 1973–2000 Period

	Males			Females		
Exposure	Total No. of ESRD Cases (total no. exposed)	No. of Exposed ESRD Cases	Cox Regression Adjusted* HR and (95% CI) 1973–2000	Total No. of ESRD Cases (total no. exposed)	No. of Exposed ESRD Cases	Cox Regression Adjusted* HR and (95% CI) 1973–2000
Trichloroethylene	53 (5,550)	46	1.91 (0.86–4.23)	18 (982)	10	1.89 (0.74–4.83)
1,1,1-trichloroethane	28 (2,092)	21	2.34 (0.99–5.52)	9 (96)	1	2.40 (0.30–19.21)
JP4 gasoline	34 (2,828)	27	2.26 (0.98–5.20)	13 (457)	5	2.19 (0.71–6.75)

*Multivariable Cox regression model: time variable = age; covariate = race.
Referent group for all comparisons = subjects with no chemical exposure (n = 1,470 males and n = 1,857 females).
HR indicates hazard ratio; CI, confidence interval; ESRD, end-stage renal disease.

Cox model stratified by 5-year calendar bands and by 5-year follow-up bands, confidence intervals were wide and none of the relative risks were statistically significant in individual strata (data not shown).

In evaluation of the full follow-up period, 1973 through 2002, none of the odds ratios in the univariable 2 × 2 table analyses and multivariable logistic regression analyses were statistically significant (Table 3), and almost all were less than the hazard ratios for the 1973 through 2000 period. The reason for this attenuation of the associations for the full follow-up period can be seen in Table 4, which shows that the rate of ESRD in TCE-exposed subjects was usually higher than the rate of ESRD in unexposed subjects each year between 1973 and 2000, but in 2001, the rate of ESRD increased sharply in the unexposed group while remaining approximately constant in the TCE-exposed group. The rate of ESRD in the unexposed group was also higher in 2002 than in earlier years, although it was lower than the rate in 2001 (note: we had ESRD incidence data only through September 2002 and the rates for both the exposed and unexposed groups might differ with a full

TABLE 3
Total Number of ESRD Cases (total number exposed), Number of Exposed ESRD Cases, and Results of 2 × 2 Table Analyses and Adjusted Logistic Regression Analyses by Hydrocarbon Exposure, With 95% Confidence Intervals, 1973–2002 Period

Exposure	Total No. of ESRD Cases (total no. exposed)	No. of Exposed ESRD Cases	2 × 2 Table* Unadjusted OR and (95% CI) 1973–2002	Logistic Regression Adjusted† OR and (95% CI) 1973–2002
Trichloroethylene	83 (6,532)	61	1.42 (0.87–2.31)	1.43 (0.84–2.44)
1,1,1-trichloroethane	45 (2,188)	23	1.60 (0.89–2.87)	1.53 (0.75–3.11)
Methylene chloride	33 (1,099)	11	1.52 (0.73–3.14)	1.41 (0.64–3.13)
O-dichlorobenzene	29 (834)	7	1.27 (0.54–2.99)	1.39 (0.54–3.60)
Acetone	39 (2,030)	17	1.27 (0.67–2.40)	1.13 (0.56–2.27)
Toluene	31 (1,669)	9	0.81 (0.37–1.77)	0.72 (0.32–1.62)
Xylene	23 (81)	1	1.88 (0.25–14.10)	1.11 (0.14–9.06)
Methylethyl ketone	29 (1,533)	7	0.69 (0.29–1.62)	0.62 (0.26–1.50)
Isopropyl alcohol	40 (2,154)	18	1.27 (0.68–2.37)	1.27 (0.62–2.59)
Other alcohols	25 (694)	3	0.65 (0.20–2.19)	0.67 (0.19–2.41)
Freon	38 (2,235)	16	1.08 (0.57–2.07)	1.10 (0.52–2.31)
Chloroform	25 (240)	3	1.90 (0.57–6.40)	1.69 (0.47–6.11)
Carbon tetrachloride	76 (5,974)	54	1.37 (0.83–2.25)	1.37 (0.80–2.33)
Perchloroethylene	26 (593)	4	1.02 (0.35–2.97)	0.98 (0.32–3.02)
Stoddart solvent	76 (6,102)	54	1.34 (0.82–2.21)	1.28 (0.75–2.19)
Styrene	24 (156)	2	1.95 (0.46–8.37)	1.90 (0.43–8.45)
JP4 gasoline	56 (3,285)	34	1.57 (0.92–2.69)	1.55 (0.85–2.82)
Mixed solvents	98 (8,816)	76	1.31 (0.81–2.10)	1.26 (0.76–2.10)

*The 2 × 2 table analyses provide the same odds ratios and 95% confidence intervals as the univariable logistic regression models and, therefore, only the former are reported in the table.

†Multivariable logistic regression model: covariates include race and gender.

Referent group for all comparisons = subjects with no chemical exposure (n = 3,327).

OR indicates odds ratio; CI, confidence interval; ESRD, end-stage renal disease.

12 months of follow up). The phenomenon was similar for the other exposures as well (data not shown).

We carried out separate adjusted Cox regression analyses from the 1973 through 1975 period to the 1973 through 1999 period, increasing the interval 2 years at a time to examine how early in the follow up ESRD risk may have been increased for hydrocarbon-exposed subjects (Table 5). We did not report results for calendar time periods ending before 1985, however, because there were too few ESRD cases before 1985 for robust statistical analyses. The relative risks for ESRD were elevated in all calendar time periods and statistically significant for TCE and 1,1,1-trichloroethane by the mid-1990s and for JP4 gasoline by the late 1980s. We also ran this analysis for other hydrocarbons and found a statistically significant increased relative risk by the late 1980s for both methylene chloride and isopropyl alcohol, although the relative risks attenuated and become not statistically significant by 2000. For carbon tetrachloride, there was a statistically significant increased relative risk in the 1973 through 1997 period only (hazard ratio [HR] = 2.01; 95% confidence interval [CI] = 1.00–4.03). No other hydrocarbons in this analysis had relative risks that were statistically significant (data not shown).

We also examined demographic factors to characterize and understand the change in results when 2001 and 2002 were included in the analyses. The distributions of gender and race were similar in the 1973 through 2000 period and the 2001 through 2002 period for the exposed and unexposed, and although the cohort overall was older in the latter period, there was no difference in mean age between the two groups in either period (Table 6). The mean age of the 86 ESRD cases diagnosed in the 1973 through 2000 period was 67.0 (SD = 8.8) and 76.1 (SD = 7.8) for the 15 cases diagnosed in the 2001 through 2002 period. Sixty-nine of the 86 cases (80.2%) in the 1973 through 2000 period were exposed to hydrocarbons, but only seven of 15 cases (46.7%) in the 2001 through 2002 period were exposed. Thus, older ESRD cases were less likely to have been exposed to hydrocarbons in the past. When the multivariable Cox (for the 1973 through 2000 period) and multivariable logistic (for the 1973 through 2002 period) regression models were used to evaluate ESRD risk for subjects less than age 60 years (ie, still of working age), we observed that most of the hazard ratios and odds ratios were higher than those computed for the overall cohort and that the two models provided similar estimates of the relative risk: TCE (HR = 3.72, odds ratio [OR] = 3.48), methylene chloride (HR =

TABLE 4
Annual Number (rate per million person-years) of ESRD Cases Exposed and Not Exposed to Trichloroethylene, 1973–2002 Period

Year	No. (rate‡ per million PYs) of ESRD Cases in the Trichloroethylene-Exposed Group*	No. (rate‡ per million PYs) of ESRD Cases in the No Chemical Exposure Group†
1973	0	0
1974	0	0
1975	1 (157)	0
1976	0	0
1977	2 (324)	1 (315)
1978	1 (164)	0
1979	0	1 (323)
1980	3 (510)	0
1981	2 (346)	1 (335)
1982	0	1 (342)
1983	1 (180)	0
1984	4 (735)	1 (355)
1985	2 (376)	0
1986	1 (193)	0
1987	5 (991)	0
1988	2 (406)	1 (387)
1989	4 (832)	0
1990	1 (214)	0
1991	1 (221)	2 (826)
1992	0	0
1993	2 (465)	1 (436)
1994	4 (961)	0
1995	6 (1,491)	1 (464)
1996	2 (517)	0
1997	1 (268)	1 (496)
1998	2 (558)	1 (515)
1999	5 (1,471)	2 (1,065)
2000	4 (1,235)	1 (557)
2001	4 (1,235)	5 (2,786)
2002§	1 (309)	2 (1,114)

*Number of subjects exposed to trichloroethylene = 6,532.
†Number of subjects with no chemical exposure = 3,327.
‡Denominator is the number of subjects alive and ESRD free at the beginning of each year.
§The rates for 2002 are not based on a complete year of follow up; ESRD incidence data were available only through September 2002.
ESRD indicates end-stage renal disease; PYs, person years.

3.36, OR = 3.39), carbon tetrachloride (HR = 3.50, OR = 3.60), Stoddart solvent (HR = 2.62, OR = 2.69), JP4 gasoline (HR = 2.82, OR = 2.81), and mixed solvents (HR = 3.23, OR = 2.93). None of the hazard ratios or odds ratios, however, was statistically significant.

Analysis of ESRD risk by cumulative TCE score did not show a monotonic, statistically significant trend. Subjects with 5 to 25 unit years of exposure to TCE had a statistically significant increased relative risk of ESRD for the 1973 through 2000 period (HR = 2.48; 95% CI = 1.20–5.15), but the relative risks for <5 unit years (HR = 1.73; 95% CI = 0.86–3.48) and for >25 unit years (HR = 1.65; 95% CI = 0.82–3.35) were not statistically significant.

In our analyses of specific categories of exposure to TCE for the 1973 through 2000 period, both the indirect low/intermittent (HR = 2.47; 95% CI = 1.17–5.19) and indirect peak/infrequent (HR = 3.66; 95% CI = 1.25–10.74) exposure categories were associated with a statistically significant increased risk of ESRD, but direct exposures were not. Both direct (HR = 2.40; 95% CI = 1.02–5.63) and indirect (HR = 2.50; 95% CI = 1.04–6.02) exposure to 1,1,1-trichloroethane resulted in a statistically significant increased risk of ESRD. None of the categories for mixed solvents was statistically significant.

Table 7 provides adjusted hazard ratios stratified by tertiles of person-years of exposure. No monotonic exposure–response gradients are evident except for 1,1,1-trichloroethane. However, statistically significant excesses in the second or third tertiles occurred for several hydrocarbons (ie, TCE, isopropyl alcohol, Freon, chloroform, carbon tetrachloride, Stoddart solvent, styrene, and JP4 gasoline), and the test for linear trend was statistically significant for TCE, 1,1,1-trichloroethane, isopropyl alcohol, carbon tetrachloride, Stoddart solvent, and JP4 gasoline.

We evaluated rates of death resulting from alcoholic liver disease, diabetes, and ischemic heart disease among hydrocarbon-exposed subjects and subjects with no chemical exposure as a surrogate for SES. There was no statistically significant difference in death rates resulting from alcoholic liver disease (0.4% vs 0.4%, $P = 0.96$) or diabetes (1.7% vs 1.4%, $P = 0.28$), but there was a statistically significant difference in deaths resulting from ischemic heart disease (17.8% vs 14.4%, $P < 0.0001$). In the multivariable Cox model, for hydrocarbon-exposed subjects compared with subjects with no chemical exposure, there was no statistically significant increased risk of death resulting from alcoholic liver disease (HR = 0.79; 95% CI = 0.43–1.47) or diabetes (HR = 1.27; 95% CI = 0.93–1.74); however, there was a slight but statistically significant increased risk of death resulting from ischemic heart disease (HR = 1.11; 95% CI = 1.01–1.22). From these data, it appears that diseases with known SES gradients did not differ substantially between our exposed and unexposed groups and, therefore, it is possible that ESRD

TABLE 5
Results of Adjusted Cox Regression Analyses for ESRD by Selected Hydrocarbon Exposure, With 95% Confidence Intervals, 1973–1985 Period to 1973–1999 Period

Period	Cox Regression Adjusted* HR and (95% CI) for Trichloroethylene	Cox Regression Adjusted* HR and (95% CI) for 1,1,1-trichloroethane	Cox Regression Adjusted* HR and (95% CI) for Methylene Chloride	Cox Regression Adjusted* HR and (95% CI) for Isopropyl Alcohol	Cox Regression Adjusted* HR and (95% CI) for JP4 Gasoline
1973–1985	2.00 (0.70–5.72)	2.17 (0.52–9.05)	3.05 (0.73–12.75)	1.94 (0.38–9.93)	1.77 (0.50–6.33)
1973–1987	2.45 (0.89–6.75)	2.98 (0.80–11.12)	**4.22 (1.15–15.43)**	3.43 (0.92–12.86)	2.54 (0.80–8.07)
1973–1989	2.37 (0.95–5.93)	2.79 (0.87–8.96)	**3.68 (1.13–11.99)**	**3.45 (1.10–10.87)**	**3.05 (1.10–8.42)**
1973–1991	1.96 (0.86–4.46)	2.41 (0.79–7.32)	**3.11 (1.02–9.49)**	**3.02 (1.06–8.58)**	**2.58 (1.04–6.43)**
1973–1993	1.77 (0.81–3.86)	2.01 (0.72–5.63)	2.55 (0.87–7.53)	2.41 (0.88–6.58)	2.13 (0.88–5.15)
1973–1995	**2.12 (1.03–4.39)**	**3.12 (1.17–8.28)**	**3.20 (1.22–8.38)**	**2.86 (1.15–7.12)**	**2.75 (1.24–6.08)**
1973–1997	**2.16 (1.08–4.34)**	**2.95 (1.13–7.71)**	**3.02 (1.17–7.79)**	**2.67 (1.09–6.54)**	**2.64 (1.23–5.70)**
1973–1999	**1.92 (1.03–3.59)**	**2.37 (1.02–5.49)**	**2.42 (1.01–5.78)**	2.02 (0.89–4.59)	**2.41 (1.21–4.81)**

Values in bold are statistically significant ($P < 0.05$).
*Multivariable Cox regression model: time variable = age; covariates include race and gender.
Referent group for all comparisons = subjects with no chemical exposure (n = 3,327).
HR indicates hazard ratio; CI, confidence interval; ESRD, end-stage renal disease.

TABLE 6
Hill Air Force Base Cohort Demographics by Exposure Status to Trichloroethylene, 1973–2000 Period and 2001–2002 Period

	Subjects Exposed to Trichloroethylene	Subjects With No Chemical Exposure
1973–2000 period	n = 6,532	n = 3,327
Percent male	85.0%	44.2%
Percent white	97.0%	97.8%
Mean age (SD) in 1973	52.78 (10.19)	53.04 (11.52)
2001–2002 period	n = 3,099	n = 1,717
Percent male	86.7%	37.7%
Percent white	96.9%	97.3%
Mean age (SD) in 2001	75.26 (6.30)	74.57 (7.14)

SD indicates standard deviation.

risk did not differ by SES either. We cannot be certain, however, and, thus, SES as a confounder cannot be ruled out in our study.

Discussion

This is the first occupational cohort study we know of that has examined the association specifically between hydrocarbon exposure and ESRD. In 1997, Calvert et al[24] published the first epidemiological study of ESRD incidence in an occupational cohort (silica-exposed gold miners), and their study provided the concept for ours. We found a statistically significant increased risk of ESRD for several hydrocarbons: TCE, 1,1,1-trichloroethane, and JP4 gasoline for the period 1973 through 2000, and relative risks were elevated, although not statistically significant, for most other hydrocarbons during this period (this may have resulted in the relative risk for mixed solvents being not statistically significant as well). Both men and women were at increased risk from exposure. Some findings, however, complicate the interpretation. First, the relative risks attenuated for TCE, 1,1,1-trichloroethane, and JP4 gasoline were not statistically significant when we included ESRD cases occurring in 2001 and 2002 in the analyses. Associations attenuated for all other hydrocarbons as well. Second, clear monotonic exposure–response gradients were not observed for any hydrocarbon except 1,1,1-trichloroethane.

We found that the attenuation of the relative risks for ESRD when 2001 and 2002 were included in the analyses occurred primarily because the rate of ESRD increased sharply in the unexposed group and not because the rate decreased in the exposed group (see Table 4; data are shown for TCE, but a similar phenomenon occurred for the other hydrocarbons as well). The rates of ESRD of 1235 and 309 per million person-years in the TCE-exposed group in 2001 and 2002, respectively, were comparable to the rates in previous years which ranged from zero to 1491 per million person-years. However, the rates of ESRD of 2786 and 1114 per million person-years in the unexposed group in 2001 and 2002, respectively, were substantially greater than the rates in previous years, which ranged from zero to 1065 per million person-years. It appears that 2001 is more anomalistic than 2002, although as noted earlier, the rates for 2002 are not based on a complete year of follow up and so it is difficult to say if the phenomenon is isolated to 2001 or if it includes 2002. It was not clear why this sudden increase among the unexposed occurred, whereas there was no change among the exposed; distributions of gender and race were the same in the 1973

TABLE 7
Results of Adjusted Cox Regression Analyses for ESRD by Tertiles of Person-Years of Hydrocarbon Exposure, With 95% Confidence Intervals, 1973–2000 Period

Exposure	Cox Regression Adjusted* HR and (95% CI) 1973–2000 1st Tertile of PYs	Cox Regression Adjusted* HR and (95% CI) 1973–2000 2nd Tertile of PYs	Cox Regression Adjusted* HR and (95% CI) 1973–2000 3rd Tertile of PYs
Trichloroethylene	<2.5 yrs	2.5–10 yrs	>10 yrs
	1.99 (1.00–3.97)	1.52 (0.72–3.21)	**2.05 (1.01–4.17)‡**
1,1,1-trichloroethane	<4.5 yrs	4.5–9.5 yrs	>9.5 yrs
	1.58 (0.52–4.75)	2.47 (0.94–6.47)	**2.98 (1.14–7.78)§**
Methylene chloride	<0.5 yr	0.5–3 yrs	>3 yrs
	4.31 (1.65–11.28)	0.59 (0.08–4.57)	1.78 (0.48–6.54)
O-dichlorobenzene	<0.5 yrs	0.5–2.5 yrs	>2.5 yrs
	2.65 (0.71–9.84)	0.93 (0.12–7.29)	1.75 (0.36–8.47)
Acetone	<1.5 yrs	1.5–5 yrs	>5 yrs
	1.95 (0.73–5.18)	0.95 (0.27–3.37)	2.26 (0.91–5.62)†
Toluene	<1.5 yrs	1.5–5.5 yrs	>5.5 yrs
	0.74 (0.17–3.27)	0.78 (0.18–3.44)	1.63 (0.56–4.72)
Xylene	<0.5 yrs	0.5–2 yrs	>2 yrs
	NA	6.82 (0.83–56.36)	NA
Methylethyl ketone	<1 yr	1–5 yrs	>5 yrs
	0.41 (0.05–3.17)	0.45 (0.06–3.43)	1.82 (0.61–5.42)
Isopropyl alcohol	<1.5 yrs	1.5–5.5 yrs	>5.5 yrs
	1.70 (0.58–4.99)	1.05 (0.29–3.84)	**2.92 (1.17–7.30)‡**
Other alcohols	<1 yr	1–3 yrs	>3 yrs
	1.06 (0.13–8.48)	NA	2.04 (0.43–9.59)
Freon	<1.5 yrs	1.5–6 yrs	>6 yrs
	1.00 (0.27–3.65)	1.00 (0.27–3.67)	**2.92 (1.15–7.40)†**
Chloroform	<2.5 yrs	2.5–5.5 yrs	>5.5 yrs
	2.80 (0.35–22.63)	**4.95 (1.05–23.31)**	NA
Carbon tetrachloride	<1.5 yrs	1.5–2.5 yrs	>2.5 yrs
	1.26 (0.57–2.80)	**2.17 (1.08–4.33)**	1.83 (0.91–3.70)‡
Perchloroethylene	<0.5 yrs	0.5–2.5 yrs	>2.5 yrs
	1.79 (0.39–8.11)	NA	0.93 (0.12–7.32)
Stoddart solvent	<1.5 yrs	1.5–5 yrs	>5 yrs
	1.23 (0.56–2.71)	**2.24 (1.14–4.41)**	1.46 (0.69–3.09)‡
Styrene	<0.5 yrs	0.5–3.5 yrs	>3.5 yrs
	NA	**7.54 (1.70–33.32)**	NA
JP4 gasoline	<1 yr	1–3.5 yrs	>3.5 yrs
	2.21 (0.97–5.02)	1.57 (0.61–4.02)	**3.20 (1.41–7.27)§**
Mixed solvents	<3.5 yrs	3.5–12.5 yrs	>12.5 yrs
	1.76 (0.91–3.40)	1.50 (0.76–2.98)	1.52 (0.77–3.01)

Values in bold are statistically significant ($P < 0.05$).
*Multivariable Cox regression model; time variable = age; covariates include race and gender.
Mantel linear trend test: †$P < 0.10$; ‡$P < 0.05$; §$P < 0.01$.
Referent group for all comparisons = subjects with no chemical exposure (n = 3,327).
HR indicates hazard ratio; CI, confidence interval; ESRD, end-stage renal disease; PYs, person-years of exposure; NA, not available because of small cells.

through 2000 period and the 2001 through 2002 period, and there was no difference in mean age between the exposed and unexposed groups in either period (see Table 6). The increase in unexposed cases in 2001 and 2002 and the resulting attenuation of the associations for the 1973 through 2002 analyses could be simply the result of chance. There were relatively few ESRD cases in 2001 and 2002 in our study—five in the TCE-exposed group and seven in the unexposed group. Of the 83 ESRD cases over the full follow-up period who had TCE exposure or who were unexposed, this represents only a small proportion (14.5%). Of course, the observed excesses for the 1973 through 2000 period could be the chance finding. This is less likely, however, because we observed consistently elevated and statistically significant relative risks for TCE and several other hydrocarbons for a number of time periods as far back as the late 1980s and mid-1990s (see Table 5). A second possible explanation that must be considered is confounding resulting from comor-

bidities. The cohort is aging (mean age in 2000 is 75 years) and the prevalence of diabetes and hypertension is undoubtedly increasing. These two systemic diseases are the number one and number two causes, respectively, of ESRD.[1] We had no data on the medical history of the cohort to confirm that there was a high prevalence of these diseases, but it has recently been reported in the United States that more than 50% of persons age 65 to 75 years have hypertension[25] and approximately 15% of persons age 70 years and older have diabetes.[26] We would not expect, however, for the prevalence of these conditions to materially differ in the exposed and unexposed portions of the cohort because we used an internal control group. A third possible explanation may be that exposure to hydrocarbons accelerates the progression of ESRD in those predisposed to develop chronic kidney disease but does not increase the number occurring. This could have yielded higher rates among younger members of the exposed portion of the cohort (as we observed) that was eventually evened out by older members of the unexposed portion of the cohort.

In a metaanalysis of 14 published case–control studies of hydrocarbons, Ravnskov reported that the mean weighted odd ratios for exposure to hydrocarbons for patient groups with outcomes of acute and/or early chronic glomerulonephritis, CRF, and ESRD were 0.95 (95% CI = 0.6–1.4), 3.1 (95% CI = 1.5–6.2), and 5.9 (95% CI = 3.8–9.3), respectively.[4] The author suggested that the results of the case–control studies of hydrocarbon-associated glomerulonephritis are better explained by the hypothesis that exposure to hydrocarbons may worsen renal function as opposed to hydrocarbons being directly causal, although the latter cannot be ruled out. The positive associations with ESRD for several hydrocarbons from our study are consistent with the results from the metaanalysis; however, our Cox model hazard ratios for ESRD were lower than Ravnskov's metaanalysis summary odds ratio for ESRD. There are several possible explanations for why our results differ, and caution should be exercised in trying to compare our relative risks directly with those from past studies. First, and most importantly, our outcome was not the same as the outcomes in the case–control studies Ravnskov included in his metaanalysis. Three of the studies[27–29] examined ESRD as a result of glomerulonephritis, whereas we studied all-cause ESRD. In the case–control study by Steenland et al[30] that included a somewhat more broad case definition of ESRD—glomerulonephritis, interstitial kidney disease, or nephrosclerosis—the odds ratios (ranging from 1.5–2.5 for solvents) are comparable to our hazard ratios. In addition, controls in these studies varied, ranging from community-based referents to hospital patients with or without other renal diseases. A second possible explanation could be that Ravnskov excluded patient groups with 5% or more dropouts resulting from death to account for the bias that can occur in case–control studies of glomerulonephritis if exposed cases are overrepresented among dropouts. We studied ESRD incidence only and did not consider the potential impact of deaths in our analysis; if more exposed compared with unexposed subjects in our study died directly or indirectly from chronic renal disease just before ESRD, our relative risks could be underestimated. A third possible reason for the differences between studies is that age of subjects could also play a role. In the four ESRD studies included in Ravnskov's metaanalysis, the subjects' ages ranged from approximately 20 to 70 years—substantially younger than our cohort's age range of 63 to 99 years in 2000. When we restricted our analyses to younger subjects (<60 years), our hazard ratios tended to increase and move closer to the odds ratios computed by Ravnskov. Because younger subjects are more likely to be currently or recently exposed to hydrocarbons compared with older subjects, this may explain in part the difference in relative risks between our study and past case–control studies. Finally, some of this variation in relative risks from different studies would be expected from chance alone.

Because we studied all-cause ESRD, the mechanism for the increased risks we observed is uncertain. One possibility is that our findings might support a hypothesis that hydrocarbons worsen renal function in individuals with systemic diseases known to adversely affect the kidneys such as hypertension and diabetes. Almost 70% of the ESRD cases with known causes in our cohort were reported in the USRDS database to be the result of diabetes or hypertension. If we assume the causes were correctly diagnosed by the physicians and that the distributions of diabetes and hypertension were similar in the exposed and unexposed groups of our cohort (which is reasonable given our use of an internal control group), then a possible explanation for the increased risks could be that there was an interaction between hydrocarbons and hypertension and/or diabetes; hydrocarbon exposure worsened kidney function and further elevated the risk of ESRD in those already at greater risk from these systemic diseases (ie, without causing glomerulonephritis). Hydrocarbon exposure may add an immunologically mediated component to diabetic and hypertensive renal disease. In his review, Ravnskov notes that hydrocarbon exposure seems to be an important factor in other renal diseases such as diabetic nephropathy, nephrosclerosis, and in patients with renal diseases of unknown etiology.[4] Unfortunately, there was no way to assess this interaction in our study because we did not have data on the disease history for the cohort. Also, we were missing the cause for 18% of the ESRD cases, which is another reason why we cannot draw any

strong conclusions about the mechanism for the increased risk we observed.

A second possibility is that for some hydrocarbon-exposed ESRD cases in our cohort, the attribution by the diagnosing physician of the ESRD to hypertension or diabetes was incorrect, and although systemic disease was present and may have caused some underlying kidney disease, the ESRD was actually the result of unrecognized glomerulonephritis resulting from hydrocarbon exposure. Because many physicians are not trained in occupational medicine, they do not consider possible occupational etiologies when evaluating a patient.[2,31] In a recent review paper, Brautbar notes that from a toxicologic and nephrologic perspective, it makes sense that individuals with underlying kidney disease are at increased risk for developing chronic glomerulonephritis from hydrocarbon exposure.[31]

The previous case–control studies of ESRD have either not assessed exposure–response[27–29] or did not observe an exposure–response gradient.[30] It has been suggested that duration of exposure may be a poor surrogate for cumulative exposure if those with short-term exposures also had higher exposures.[30] Except for 1,1,1-trichloroethane, we likewise did not see consistent monotonically increasing risk of ESRD with increasing levels of exposure. If there are immunologically mediated mechanisms for chronic renal disease and/or if certain individuals are more genetically susceptible,[32] this might lead to patterns distinct from traditional exposure–response, but this is speculative at this time.

Our study had several strengths. First, our cohort was large with a long follow-up period. Second, the cohort design allowed for the ascertainment of the outcome after information on the exposure was obtained, thereby eliminating the risk of reporting bias. Third, the exposure assessment conducted by the NCI was based on information regarding exposure and work processes provided by the Air Force for 16 specific hydrocarbons.

Our study also had several limitations. First, despite the large sample size, there were only 101 cases of ESRD and, therefore, for analyses of individual hydrocarbons, the numbers of cases often became quite small. Second, exposures were not mutually exclusive, and with this overlap, it was not possible to evaluate the risk of ESRD from individual hydrocarbons while controlling for exposure to other hydrocarbons or chemicals used at the base. Associations were seen for a majority of hydrocarbons studied, although most were not statistically significant. Third, the study population was predominantly white (87%) and male (74%). Although results for women appeared similar to those for men for TCE, 1,1,1-trichloroethane, and JP4 gasoline, we were unable to evaluate risks among nonwhite cohort members because of small numbers. Fourth, multiple comparisons were made and some associations would be expected as a result of chance alone. Fifth, we had exposure data for the cohort for as far back as the 1940s, but we only had ESRD incidence data since 1973; thus, we missed approximately 3 decades of chronic kidney disease outcomes. Consequently, our relative risks for the hydrocarbons used predominantly at the Hill Air Force Base before 1973 such as Stoddart solvent and carbon tetrachloride may be underestimated. Also, because of this mismatch in the timing of exposure data and ESRD incidence data, we could not assess latency. Sixth, we only had ESRD incidence data through September 2002, and it is unknown if the 3 additional months needed for a full year of follow up would have changed the results. Seventh, because we had ESRD incidence data through September 2002 but we only had mortality data through December 2000, we were forced to use different statistical methods for different time periods. It would have been preferable to have mortality and ESRD incidence data for the same time periods, which would have allowed the Cox model to be used for analysis of the entire follow up. Eighth, we did not have enough cases of ESRD as a result of glomerulonephritis to analyze this outcome by itself, and we were limited to looking at all-cause ESRD. Finally, other than age, gender, and race, data on lifestyle and other nonoccupational risk factors such as hypertension, diabetes, family history of renal disease, and SES, which might confound the relationship between exposure and disease, or which might be effect modifiers, were not available for the cohort.

Conclusion

The results of this retrospective cohort study suggest that exposure to hydrocarbons may increase the risk of ESRD. The risk of ESRD in exposed compared with unexposed workers at the Hill Air Force Base was elevated for several hydrocarbons for the period 1973 through 2000. Because exposures were not mutually exclusive, however, we are limited in our ability to draw strong conclusions about risk associated with individual hydrocarbons. The sudden attenuation of the relative risks when 2001 and 2002 data were included in the analyses also dampens our confidence in the associations somewhat. In addition, because we studied all-cause ESRD, the implications of the increased risks we observed are unclear; it is possible that hydrocarbon exposure further elevated ESRD risk in those already at higher risk as a result of underlying diseases such as diabetes and/or hypertension; however, the mechanism is uncertain. A future study of the cohort with extended follow up is warranted to investigate the 2001 through 2002 issue further, and the conduct of similar studies in other large occupational cohorts with known hydrocarbon exposure, and preferably with data on other ESRD risk factors, is recommended.

Acknowledgment

This research was the doctoral thesis of Dr Radican, who is also a full-time employee of Merck & Co., Inc. This research was supported by unrestricted educational grants from Merck & Co., Inc. and the University of Medicine and Dentistry of New Jersey–School of Public Health. Dr Rhoads is supported by Center grant no. ES05022 from the National Institute of Environmental Health Sciences. This research was also supported, in part, by the Intramural Research Program of the NIH (Division of Cancer Epidemiology and Genetics, National Cancer Institute).

The data reported here have been supplied by the NCI, the USRDS, and the NDI. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of these organizations and/or the U.S. government.

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